required to specify the particular method used to diagnose the patient. The Specification teaches that in particular embodiments, the subject patient has undergone removal or ablation of a colorectal neoplasia and is determined to be predisposed to colorectal neoplasia recurrence, including genetically predisposed to the development of colorectal neoplasia (Specification, p.4, lines 17-19); that preferred target patients are predetermined to have a personal or familial history of colorectal neoplasia, or are predetermined to be at relatively high risk of developing a colorectal neoplasia (Specification, p.4, lines 20-22); and that the determining step may comprise detecting an indication of or predisposition to polyps or colorectal cancer (Specification, p.4, lines 22-23). Those skilled in the art do not require further recital to understand and practice the determining step recited in the claims.

The claims also recite relative terms such as "reducing development of," "reduced," "poor gut absorption," and "gut-beneficial culture." The claims and specification are directed to those skilled in the art; in particular those skilled at diagnosing and treating patients with colorectal neoplasia. The Specification provides detailed description of each of the recited relative terms. Furthermore, our claimed methods of "reducing" development of colorectal neoplasia expressly require that the development of colorectal neoplasia be "reduced" *as compared with otherwise similar non-treated patients*, (see, e.g. claim 1). Furthermore, detecting results whereby the development of the colorectal neoplasia is reduced as compared with otherwise similar non-treated patients is repeatedly exemplified. Specification, p.6, line 19 - p.7, line 10; p.7, lines 12 - 31; and p.8, lines 1-20.

The claims and Specification detail that the recited antibiotic provides poor gut absorption, similar to aminoglycoside antibiotics, such as neomycin. Our Specification teaches that methods for modifying or delivering otherwise highly gut absorbable antibiotics to or in a poorly gut absorbable form are known in the art, and include gut-retaining chemical moieties, chelators, enteric coatings, etc.; see, *Remington's Pharmaceutical Science*, Mack Publishing Co, NJ (1991). In addition, suitable excipients or carriers and methods for preparing administrable compositions are known or apparent to those skilled in the art and are described in more detail in publications such as *Remington's*. Specification, p.5, lines 6-15.

Claims 11 and 15-17 are dependent claims further restricting the antecedent claim to wherein the recited method further comprises introducing into the gut an effective amount of a probiotic, gut-beneficial microbial culture. The claims and specification are directed to those

skilled in the art; in particular, those skilled at diagnosing and treating patients with colorectal neoplasia. The Specification teaches embodiments of the invention which forestall or help avoid development of undesirable effects of antibiotic usage, such as side-effects, antibiotic resistance, etc. These embodiments adopt established procedures for minimizing development of side effects, resistance, etc. Specification, p.5, lines 16-19. In the immediate subsequent paragraph, the Specification teaches that in particular embodiments, the invention further comprises introducing into the gut an effective amount of a probiotic, gut-beneficial microbial culture (Specification, p.5, lines 28-29), and provides detailed description and exemplification of this embodiment. Hence, those skilled in the art would recognize the function provided by the probiotic, gut-beneficial microbial culture, and not confuse it with "an anti-neoplasia agent."

35USC103(a): Claim 1-17

Flotte et al. (US Pat No. 5,614,502) describe administering therapeutic compounds in combination with high pressure impulse transients to treat diseases like neoplasms and inflammation. Flotte Col.3, lines 14-16, 26-28. The compounds are administered so as to be preferentially localized to the target tissue. Col.3, lines 40-44. Then, high pressure waves are generated (for example, by laser-induced ablation, Col.4, lines 20-25), which increase drug delivery to localized cells. Col.4, lines 57-60. Because the drugs have little effect in the absence of the high pressure impulse, there should be little toxicity outside the area of the tumor. Col.5, lines 11-14. The high pressure impulse works by increasing cell permeability, Col.5, lines 20-22.

Hu et al. (US Pat No. 6,482,802; see, also, Hu et al. paper, 1998, PNAS 95, 9791-795) report that neomycin was the only member of a panel of aminoglycoside antibiotics that was able to reduce angiogenin-induced cell proliferation and angiogenesis, as measured using cultured human endothelial cells and chick embryo chorioallantoic membranes (CAM). Streptomycin, kanamycin, gentamicin, amikacin, and paromomycin were found to lack anti-angiogenic activity. This Hu attributes to phospholipase C (PLC) inhibition because neomycin is the only aminoglycoside antibiotic of the panel tested that inhibits PLC, and because U-73122, another PLC inhibitor, similarly inhibited angiogenin-induced cell proliferation and angiogenesis. See abstract of Hu paper; col.20, lines 22-28, col.21, line 66 - col.22, line 8, and col.27, lines 8-27 of Hu patent. The Hu patent also reports that injected neomycin was able to reduce growth of

cultured angiogenin-secreting tumor cells (Olson et al., Int J Cancer. 2002 Apr 20;98:923-9; Clin Cancer Res. 2001 Nov;7:3598-605) transplanted into mice; see, col.27, line 43 - col.29, line 10 of Hu patent.

From these findings, Hu suggests use of neomycin for treating any angiogenin-induced angiogenesis. The Hu patent purports applicability to all angiogenesis-related diseases, which are "myriad and varied" and "include, but are not limited to, various forms of neovascularization or hypervascularization diseases, inflammatory diseases, arthritis and cancer", and then goes on to recite a laundry-list of all major solid and blood-borne tumors, corneal and retinal diseases, inflammatory diseases, and various infectious diseases, including AIDS (col.16, line 56 - col.18, line 16). Among the 60+ recited solid tumors is colon cancer (col.17, lines 10-11).

Hu does not provide the public with any cure for cancer, inflammatory disease, arthritis, or AIDS. He has shown that neomycin can reduce angiogenin-induced angiogenesis and growth in CAM and cultured cell models, and from these data, claims to be able to treat innumerable human diseases. In fact, anti-angiogenesis drugs have notoriously failed to live up to their promise as cancer therapies, primarily because there are dozens of alternative factors which can drive angiogenesis. Science Journal, WSJ, Jul 11, 2003. Furthermore, reports using azoxymethane (AOM) and 1,2-dimethyl hydrazine (DMH)-induced colon cancers have suggested neomycin is not a viable therapy for colon cancer, and may actually increase the incidence of colon adenocarcinomas (Reddy et al., 1984 JNCI 73, 275-9; Panda et al., 1999, Br J Cancer 80, 1132-6).

With the recent development of colon cancer animal models based on defined genetic lesions (e.g. Zhu et al., Cell 1998, 94, 703-714), the use of chemical carcinogenesis models like AOM and DMH has become less favored (Boivin et al., Gastroenterology 2003, 124, 762-777). Hence, a recent review of colon cancer chemoprevention surveys the many agents reported to influence intestinal tumors, and does not include any antibiotics; see, Table 1 of Corpet et al., Cancer Epidemiology, Biomakers & Prevention 2003, 12, 391-400. Work in colon cancer animal models has suggested that intestinal neoplasia is independent of gut microbial status (Dove et al., Cancer Res 1997, 57, 812-14).

The present inventors made the serendipitous discovery that enterically delivered aminoglycoside antibiotics can dramatically reduce the development of colorectal carcinogenesis in defined rodent models. The inventors here clinically extend these animal model findings by

showing that enterically delivered aminoglycoside antibiotics can inhibit large bowel carcinogenesis in human patients with familial adenomatous polyposis. The inventors further extend these findings by showing that altering the population profile of gut flora, through a defined regimen of aminoglycoside antibiotic treatment and supplementation of non-target gut microbes such as Lactobacillus, is effective in preventing the formation of colorectal polyps and colorectal cancer. The inventors demonstrate prevention of spontaneous tumor formation indicating that the disclosed protocols interfere with early processes of carcinogenesis that are distinct from angiogenesis.

Our claims are properly restricted to a method of reducing development of colorectal neoplasia in a patient subject or predisposed to colorectal neoplasia, by (a) determining a patient is subject or predisposed to colorectal neoplasia; and (b) enterically delivering into the gut of the person an effective amount of an aminoglycoside antibiotic having poor gut absorption, whereby the development of the colorectal neoplasia is reduced as compared with otherwise similar non-treated patients. As noted above, prior to the present disclosure, those skilled in this art did not have an expectation that such enterically delivered aminoglycosides could provide effective therapy for colorectal neoplasia.

The Hu patent does not suggest to those skilled in the art that such enterically delivered aminoglycosides could provide effective therapy for colorectal neoplasia, and Flotte's method for using high-pressure impulse transients to promote drug delivery does not somehow complement Hu to provide such a suggestion. There is nothing in Flotte's patent that suggests that such enterically delivered aminoglycosides could provide effective therapy for colorectal neoplasia. Similarly, there is nothing in Hu's patent that suggests that enterically delivered aminoglycosides could provide effective therapy for colorectal neoplasia, so Hu can not be read to modify Flotte to provide that suggestion. We submit that this rejection presupposes and relies upon the serendipitous discovery of the present disclosure: absent our disclosure, how does one skilled in the art learn that enterically delivered aminoglycosides could provide effective therapy for colorectal neoplasia?

In any event, the proposed combination is inapplicable to the delivery protocol recited in our claims. The function of Flotte's high pressure impulse transients is to increase cellular absorption of *systemically* delivered drugs. Flotte, Col.3, lines 50-54; Col.4, lines 59-60. Aminoglycoside antibiotics having poor gut absorption are well-established for parenteral

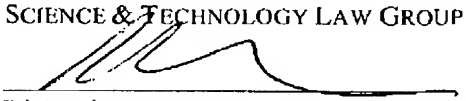
delivery, which results in systemic distribution, primarily within the extracellular fluid. Specification, p.1, lines 17-22. For such systemic delivery, the high-pressure impulse transients of Hu may well provide for the desired localized enhanced drug delivery. However, our claims are restricted to *enteric* delivery into the gut of the target patient, and our claims specifically require an aminoglycoside antibiotic having poor gut absorption. The methods of Flotte do not appear to have any application to enterically restricted drugs.

Though we do not believe the cited art supports any prima facie case for obviousness, for good measure, we append an expert Declaration from Professor Graff, averring to the foregoing facts and conclusions. Accordingly, the uncontroverted evidence of record demonstrates that the cited art would not have suggested the claimed methods to one skilled in the art at the time the invention was made.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

We petition for and authorize charging our Deposit Account No.19-0750 all necessary extensions of time. The Commissioner is authorized to charge any fees or credit any overcharges relating to this communication to our Dep. Acct. No.19-0750 (order UTSD:0980).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP



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